

Lewis Dahl and the genetics of salt-induced hypertension

In the 1960s, Lewis Dahl bred two strains of rats that differed in their susceptibility to developing salt-induced hypertension. These animal models proved that hypertension induced by a high-salt diet is influenced by genetic background.

The notion that hypertension is caused by a high-salt diet is more than a hundred years old, but much of its history is punctuated by controversy. The earliest study that reported a positive correlation between salt intake and blood pressure in humans was published in 1904 and was refuted just three years later (1). Although this ambiguity was echoed by numerous reports over the next 40 years, the validity of the link was reinforced in the 1940s when a physician named Wallace Kempner successfully treated hypertensive patients with a low-salt diet (2). Other researchers then launched population studies that measured blood pressure in response to the level of salt ingestion.

Genetic susceptibility

The population study that captured the most attention was performed by Lewis Dahl, a physician at the Brookhaven National Laboratory (Upton, NY). Dahl's unique contribution was to compare hypertension across various populations, as salt intake levels vary widely among geographically distinct groups (3). He found that hypertension was common in societies with higher-than-average salt intakes. In contrast, hypertension was rarely seen in populations that consumed low-salt diets. Dahl also observed that every population included individuals who consistently consumed excess salt but did not develop hypertension. He therefore argued that the development of hypertension depends on both environmental factors (e.g., salt) and the individual's genetic background.

Results from animal studies backed up his hypothesis. Over a period of 15 years, Dahl observed that only three-fourths of rats chronically fed with a high-salt diet developed varying degrees

of hypertension (4). Salt-resistant animals, however, might simply have been statistical outliers within a genetically homogeneous group. Dahl reasoned that, if salt sensitivity was a genetic trait, it would be possible to develop separate strains of salt-sensitive and salt-resistant rats.

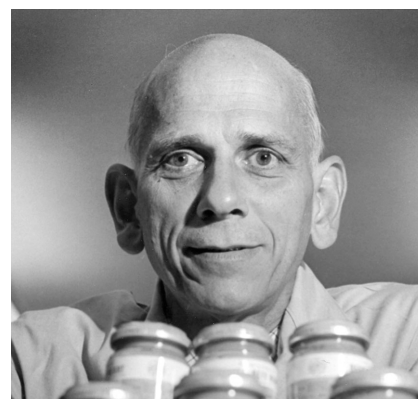
Selecting for sensitivity

Dahl began a breeding program in which rats were fed highly salted food to generate easily discernable differences in blood pressure. Rats either remained healthy or developed high blood pressure within four weeks. Dahl then crossed animals within each of the two groups, and after only 3 generations, the salt-sensitive (S) and salt-resistant (R) rat lines were clearly separated. The blood pressure of R rats remained the same when they were switched from a control diet to a high-salt diet. But in S rats, this switch induced a deadly increase in blood pressure. S rats that were maintained on a control diet did not develop hypertension, proving that the right diet can keep hypertension at bay even in susceptible individuals. These seminal results were published in the *Journal of Experimental Medicine* in 1962 (5).

The new model delivers

Dahl's work over the next 10 years resulted in several improvements in diet-based control of hypertension in humans. He found that salt-induced blood pressure in S rats could be reduced by increasing dietary potassium levels (6)—now a successful treatment option for many hypertensive patients in conjunction with a low-salt diet. He also demonstrated the dangers of high salt content in processed baby food when he showed that this food induced fatal hypertension in S rats (7).

Salt reduction regimens have been controversial within the hypertension



Lewis Dahl

field, as skeptics questioned whether these diets will be universally beneficial. Dahl's work, which emphasizes the interaction between gene and environment in raising blood pressure, gives reduction therapy a strong endorsement. "We can't change people's genes," says epidemiologist Paul Elliott. "But we can certainly change their environment to lower their risk [for hypertension]."

Dahl also left another legacy: Dahl rats are still used in the search for hypertension-responsive genes and genetic markers of salt sensitivity. Linkage analyses and mapping studies have so far yielded 16 regions in the S rat genome that may contain genes that regulate hypertension (8). The single gene identified so far encodes 11 β -hydroxylase, an enzyme required for the synthesis of a steroid that stimulates salt retention. It's their allele of this gene that gives S rats their hypertension (9).

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